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Mechanism of the antihypertensive Effects of diuretics

Possible role of salt in hypertension

The mechanism of the antihypertensive effect of chlorothiazide does not differ from that of such potent salt-depleting therapeutic agents as the mercurial diuretics and the rice diet. The extracellular fluid and plasma volumes are reduced and, as a result, right heart filling pressure, cardiac output, and blood pressure (if abnormally elevated by some pressor stimulus) fall. Because of the reduction in plasma volume, drugs which increase the capacity of the peripheral vasculature, such as ganglioplegic agents, synergize with chlorothiazide. The reasons for some of the contradictory interpretations of chlorothiazide activity are discussed and appear to be due primarily to (1) the difficulty in assessing antihypertensive mechanisms in long-term studies and (2) confusion over the significance of "normal" values for total exchangeable sodium in chronic experiments with chlorothiazide. For the reasons stated, it is suggested that salt plays a permissive rather than a primary etiological role in the genesis of essential hyptertension.

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Clarification of the mechanism of the antihypertensive effects of chlorothiazide and its congeners is of considerable interest and importance. The clinical value of chlorothiazide in hypertension has been demonstrated by its effectiveness in reducing blood pressure particularly when administered in conjunction with other antihypertensive agents.[6,8] The wide margin between effective and toxic doses permits simplified dosage schedules and insures relative freedom from unpleasant side effects.[7] The complicating side action of hypokalemia appears to be manageable with potassium supplementation and the only sensitization reaction of any moment has been an occasional case of dermatitis.

Unlike other antihypertensive agents, chlorothiazide lowers blood pressure exclusively in hypertensive and not in normotensive individuals.[8,30] The selective antihypertensive action raises the question as to whether the drug is a specific antagonist of the etiological factors producing hypertension.[30] The present paper reviews some of the evidence pertaining to the mechanisms

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of the antihypertensive effects of chlorothiazide and concludes that the principal mechanism of the antihypertensive effect is an alteration in reactivity. The alteration appears to be brought about by a change in the pressure-volume relationship of the vascular system and the blood volume which is a consequence of the saluresis.

It has been known for some time that low sodium diets increase the effectiveness of various antihypertensive procedures.[9,27] It also has been a common observation that the diuresis associated with parenteral mercurials could precipitate hypotensive collapse in hypertensive cardiac patients who were taking ganglion-blocking drugs. When it became apparent that oral chlorothiazide approached the diuretic potency of parenteral mercurials it was a natural step to test its value in the treatment of nonedematous hypertensive patients. The results of the preliminary trials, submitted as an abstract to the American Heart Association in June, 1957, indicated that chlorothiazide enhanced the antihypertensive activity not only of ganglion-blocking drugs but also of hydralazine and Veratrum.[9] These clinical observations lead naturally to an examination of the extent of the salt depletion produced by chlorothiazide in nonedematous patients.

Saluretic action in nonedematous patients

Nonedematous, hospitalized, hypertensive patients were placed on a constant daily ration of 4.25 Gm. of salt per day. After the basal daily excretion of urinary electrolytes on this intake was determined, chlorothiazide was administered in a dose of 500 mg. orally 3 times daily. During the first 3 to 4 days after the drug was given, there was an excretion of approximately 250 mEq. of sodium, 400 mEq. of chloride, and 150 mEq. of potassium over and above the basal level of excretion.[8,31,32] Following the initial diuresis the saluretic effect tapered off. Output came back into balance with intake but the deficit was not restored by a period of positive balance. Thus, the initial losses of body stores of sodium and chloride were maintained for at least one to 2 weeks of continuous treatment.[11] The serum concentrations of sodium and chloride remained unchanged. Potassium concentration often fell moderately and this reduction tended to deepen as treatment was continued over a period of months.

Plasma and extracellular fluid depletion

The 250 mEq. of sodium lost from body stores must come either from the cells or interstitial fluids. Total extracellular fluid volume, as estimated by the changes in available thiocyanate space, decreased by about 2 L.[7,31,32] Since body weight declined by an average amount of 1.8 kilograms it was apparent that the extracellular fluid loss could account for the change in body weight without implicating the intracellular fluid volume.[32] Furthermore, since the serum concentration of sodium was essentially unchanged it could be concluded that extracellular isotonicity to sodium was unaltered. The net effect of chlorothiazide administration in nonedematous patients, therefore, is similar to that observed in edematous individuals except that the mobilizable pool of extracellular fluid is considerably smaller in the former. Cellular extraction of potassium also was apparent since the excretion of this electrolyte was above the amount present in 2 L. of extracellular fluid.

Since the interstitial fluid spaces and the plasma volume are in equilibrium, it was not surprising that there was a reduction in the latter, the reduction averaging approximately 350 ml. There also was a corresponding rise in hematocrit reflecting the hemoconcentration.[8,31,32] Similar changes in plasma volume have been observed by others.[4,28]

Relationship between decrease in plasma volume and antihypertensive effects of chlorothiazide

It is well known that depletion of blood volume by even small amounts will enhance

the antihypertensive effects of certain agents, particularly ganglion-blocking agents.[12] For example, in hypertensive patients treated with ganglion-blocking drugs, withdrawal of as little as 2 to 4 per cent of the total blood volume resulted in perceptible additional decrements of arterial pressure.[13] O'Donnell[22] demonstrated a reduction in plasma volume in hypertensive patients treated for several weeks with Kempner's rice and fruit diet. O'Donnell was able to reverse the postural hypotensive effects of the rice diet either by administering salt or else by replenishing the plasma volume with salt-free dextran solutions. It has also been noted that parenteral mercurials (which likewise are potent saluretic agents) increase the responsiveness to antihypertensive drugs; reduce blood pressure in hypertensive patients[17] but not in normotensive

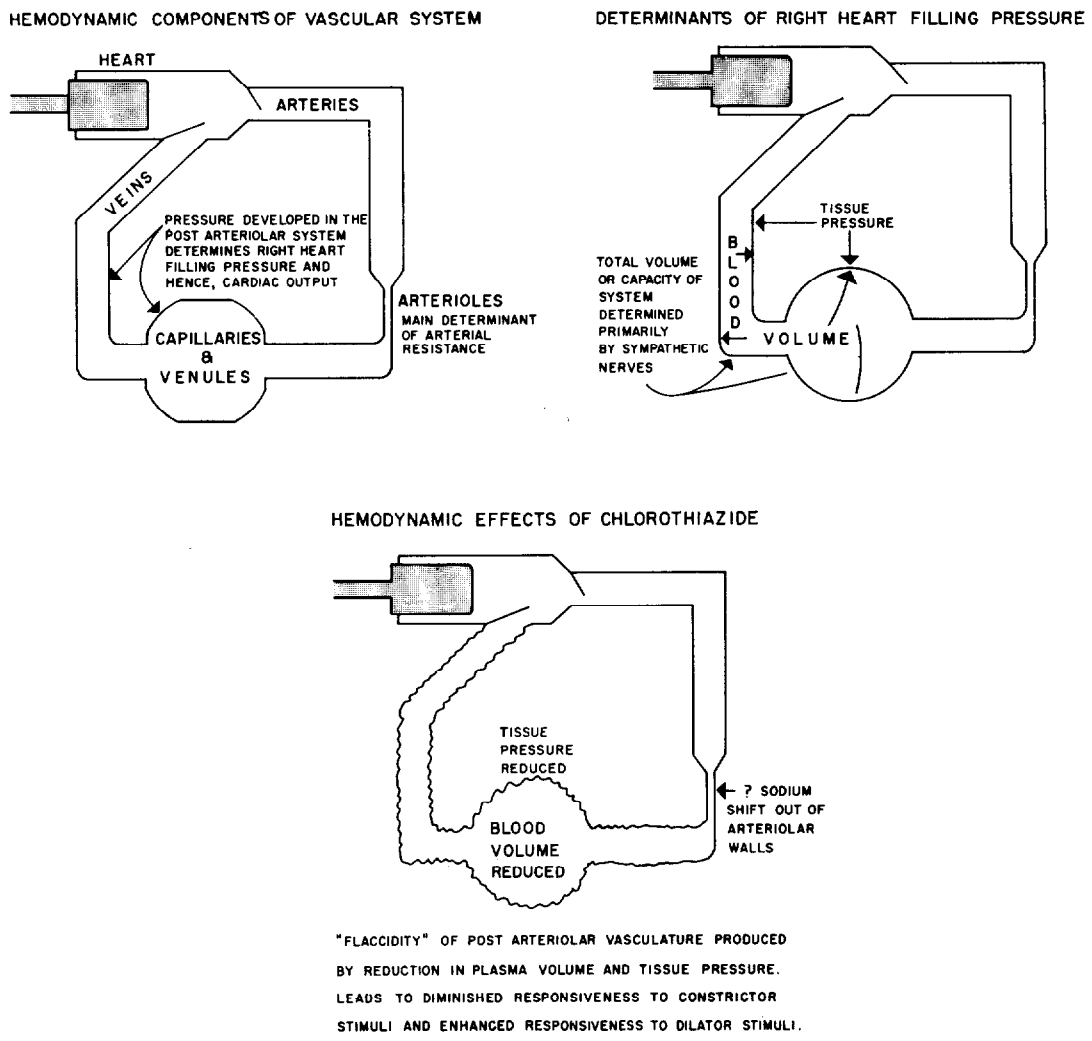

Fig. 1. Schema of proposed concept of the mechanism of the antihypertensive effect of chlorothiazide. Other factors influencing right heart filling pressures and cardiac output, such as myocardial "contractility," pulmonary and systemic peripheral resistance, etc., have been omitted only because they do not pertain to the concept developed in this review. This is not to deny their importance in other circumstances.

subjects[19]; and diminish plasma and extracellular fluid volumes in nonedematous individuals.[19,20] These observations pointed the way for further experiments with chlorothiazide.

If depletion of plasma volume was important in the antihypertensive effect of chlorothiazide, then restoration of the plasma volume should reverse the process. This was indeed the case. Hypertensive patients under hospital control conditions and a constant daily intake of salt exhibited reductions in basal arterial pressure with chlorothiazide alone which averaged approximately 15 per cent less than the pretreatment "mean" $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ blood pressure.[14] When 500 ml. of 6 per cent dextran was infused intravenously over a 15 minute period, the blood pressure rose to approach the pretreatment level.[10,11] Administration of salt was not important in this response as comparable elevations were seen when the dextran was administered either in isotonic saline solution or in 5 per cent glucose in water.[11,32] These observations have been confirmed recently by Dollery and co-workers.[4]

The relationship between the vascular capacity and the contained blood volume seems to be important in this antihypertensive effect. Crosley and his associates[3] have shown and we[11] have confirmed that the hypotensive response to chlorothiazide is associated with a decrease in right heart pressures and in cardiac output as estimated by the Fick principle. Crosley found, in addition, that if the lower extremities were elevated in order to increase the venous return, the cardiac output rose. Dustan and her co-workers[5] using the dye method found a decrease in cardiac output after chlorothiazide. This was reversed by infusion of salt-free dextran.

These observations permit the formulation of a concept of the mechanism of the antihypertensive effects of chlorothiazide and other salt-depleting agents. It is convenient to postulate a labile reserve of total extracellular fluid and plasma volume which are in equilibrium. The amount is approximately 2 L. in nonedematous individuals who have free access to salt in the diet. This reserve of extracellular fluid can be mobilized by severe salt restriction, by potent saluretic agents, or by any event producing dehydration. (It may be noted that drastic purgation, a popular method of treating acute forms of hypertension in bygone days, produces the same effect). The resulting decrease in plasma volume and probably also of tissue pressure impairs the venous return of blood to the heart with a consequent fall in cardiac output and, hence, arterial pressure. Ganglion-blocking drugs also decrease venous filling pressures and cardiac output, but they affect the other member of the relationship between vascular capacity and blood volume. After blocking drugs, the blood volume remains unchanged but the peripheral vascular capacity increases thereby reducing right heart filling pressures.[26] These interrelationships explain the synergism between the hypotensive effects of chlorothiazide and the ganglion-blocking agents.

Effects of chlorothiazide on blood pressure responsiveness

In discussion of the changes produced by chlorothiazide on the effects of pressor and depressor agents, it is preferable to use the terms "blood pressure responsiveness" or simply "reactivity" to "vascular reactivity." The latter phrase implies a change in contractility of the smooth muscle of vascular walls, an interpretation that cannot be assumed on the basis of present evidence.

As previously mentioned, only hypertensive patients exhibit a reduction in basal blood pressure after chlorothiazide alone. Normotensive subjects with basal diastolic levels of 85 mm. Hg or less do not exhibit a significant change in blood pressure following the drug.[8] On the basis of this and other evidence, Wilkins, Hollander, and Chobanian[30] postulated that chlorothiazide and mercurials have a specific antagonistic effect on the etiological factors operative in pro-

ducing hypertension. They proposed that chlorothiazide inhibits the production of renin. Obviously chlorothiazide might provide a pharmacologic tool of some importance in exploring the nature of the difference between hypertensive and normotensive individuals.

As a preliminary to this investigation it was necessary to determine whether chlorothiazide produced a similar depletion of extracellular fluid space and plasma volume in normotensive subjects as in hypertensive patients. Following chlorothiazide in normotensive subjects who were studied under identical hospital conditions, there was an average loss of 285 mEq. of sodium over and above the level of intake during the first few days of therapy.[15] The mean decrease in body weight in these patients also was 2.0 kilograms. This was identical with the weight loss observed in the hypertensive patients. A significant decline in plasma volume was indicated in the normotensive subjects by the fact that the mean hematocrit values rose from 44.2 to 48.3 per cent. Thus, chlorothiazide did not appear to exert a different effect on sodium excretion or fluid volume compartments in normotensive and hypertensive patients.

Although chlorothiazide did not reduce the basal level of blood pressure in normal individuals, it was soon found that their blood pressure responsiveness was altered. The pressor response to agents such as norepinephrine was significantly reduced[21,29] and the depressor response to depressor agents such as trimethaphan was significantly increased.[29] The average elevation of "mean" $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ blood pressure following a given level of infusion of norepinephrine was approximately 15 per cent *less* after, as compared to before, chlorothiazide.[15,29] It is interesting that this is quantitatively similar to the average fall in *basal* blood pressure in hypertensive patients. Reduction in blood pressure responsiveness to pressor agents has also been observed in dogs after chlorothiazide[1] and other diuretic agents.[2]

In order to estimate the importance of plasma volume depletion, salt-free dextran was infused in the chlorothiazide-treated, normotensive subjects. After restoration of plasma volume, the blood pressure responsiveness of these normotensive subjects returned in some cases completely to the control value. Thus, the change in reactivity induced by chlorothiazide seemed to be dependent in large measure on plasma volume depletion.

This observation may explain the differing effects of chlorothiazide on the basal blood pressure of hypertensive and normotensive subjects. If the fall in plasma volume (and possibly tissue pressure) diminishes reactivity to any pressor stimulus, then chlorothiazide also would diminish the response to the unknown pressor agent or agents which produce essential hypertension. Thus, chlorothiazide or any salt-depleting agent reduces blood pressure only when some abnormal hypertensive stimulus is operative. In this respect, its action is nonspecific. Pressor responses of all types are dampened and diminished but not specifically antagonized in the metabolic sense that Wilkins and Hollander[30] proposed.

It is significant that the basal blood pressure was reduced by chlorothiazide in hypertensive patients with diastolic levels as low as 90 mm. Hg.[11] Such results do not support Pickering's[25] thesis that hypertensive patients with only moderate elevations of arterial pressure represent merely the higher ranges of normal blood pressure in the total population. The difference in the response of the basal blood pressure to chlorothiazide when it is above or below 90 mm. Hg suggests that we are dealing with two distinct populations.

Antihypertensive effect of chlorothiazide after long-term treatment

Much of the difference of opinion concerning the mechanism of the antihypertensive effect of chlorothiazide is based on the difference in results obtained in short-term and long-term experiments. After several

months of continuous daily treatment the depletion of total extracellular and plasma volume tends to disappear and after 6 months or one year no significant difference from control values can be found.[32] The reason for this is not clear. For want of a better explanation we have ascribed this to the development of tolerance. In most instances, however, the blood pressure continues to be depressed. This has been the most cogent argument for a specific antihypertensive effect of chlorothiazide distinct from its saluretic action.[30,33] It implies, however, that the drug reduces blood pressure by one mechanism initially and by an entirely different mechanism at a later date.

Another explanation which fits with observations made on the long-term effects of other antihypertensive agents[24] is that the severity of the hypertension decreases after long-term control at lower levels of blood pressure. The reason for this modification of the hypertensive process is not known although there is evidence that the baroreceptor mechanisms can be reset if blood pressure is maintained at a different level for weeks or months.[23] Thus, in order to prove that chlorothiazide still is exerting an antihypertensive effect after long-term treatment, the drug should be withdrawn for some time in order to determine whether the blood pressure will rise to the pretreatment level. In any event, it is difficult to assess the long-term hypotensive mechanisms of antihypertensive agents.

Another discrepancy in the interpretation of the antihypertensive action of chlorothiazide can be traced to a confusion between the estimation of total extracellular fluid space and total exchangeable sodium. The latter provides an estimate of both extracellular and intracellular sodium which can be exchanged with isotopically labeled sodium over a defined period of time, usually 24 hours. The space so measured is considerably larger than the extracellular fluid volume and includes most of the sodium in the body except that which is fixed in bone. In addition, chlorothiazide produces a continuous potassium loss and if the dietary intake of this ion is not ample, a gradual depletion of potassium will occur. Under these circumstances sodium will move into the cells to make up the potassium deficit. Thus, in the studies of Hollander[17] and Winer[33] where total exchangeable sodium was estimated, sporadic results might be expected especially since the experimental measurements were made in outpatients after several weeks or months of treatment. For example, if potassium intake was poor in a given patient, the total extracellular space and plasma volume could be reduced but the value for total exchangeable sodium would be normal because of accumulation of exchangeable sodium in the cells. In addition it is impossible to be certain with outpatients that the prescribed medications are being taken faithfully. It is not too surprising, therefore, that these authors failed to observe a significant correlation between total exchangeable sodium and antihypertensive effect.

Much has been written on the significance of sodium in the genesis of essential hypertension. Most of the valid human evidence on which this supposition is based has to do with antihypertensive effects of salt-depleting procedures. Salt in this situation appears to have no specific etiological significance, however. Its action rather is permissive in that by allowing "normal" expansion of plasma and total extracellular fluid volumes the unknown pressor factors in hypertension can operate more effectively than when these fluid spaces are contracted.

It is entirely possible, of course, that the sodium ion may play an important role in smooth muscle contractility and by this means exert an additional influence in hypertension. However, the data available on this subject are so conflicting that as yet no guiding concepts can be defined.[16] Whatever the role of sodium in vascular reactivity and in hypertension may turn out to be, we cannot neglect the simple relationship of this ion to the maintenance of normal plasma and extracellular fluid volumes and the importance of these to blood pressure responsiveness.

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